An efficient solvent-free synthesis of meso-substituted dipyrromethanes using SnCl$_2$·2H$_2$O catalysis

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ABSTRACT: Highly rapid and simple methodology has been developed for the quantitative synthesis of meso-substituted dipyrromethanes from lowest pyrrole/aldehyde ratio. The method was carried out by using SnCl$_2$·2H$_2$O as a catalyst under solvent free condition. The method is environmentally friendly, easy to workup, and gives excellent yield of the products.

Keywords: pyrrole; dipyrromethanes; SnCl$_2$·2H$_2$O catalysis; grinding

Introduction

Dipyrromethanes are important building blocks for the synthesis of porphyrins [1], Calixpyrrols [2], and Corroles [3]. Dipyrromethanes are compounds known for more than a century [4]. In the past decades, a variety of conditions have been established for the synthesis of dipyrromethanes in the presence of various catalysts such as p-toluenesulfonic acid [5], TiCl$_4$ [6], CF$_3$COOH [7] and pyrrolidinium tetrafluoroborate [8]. In the synthesis of dipyrromethanes most of the conditions are based on the acid catalyzed condensation of pyrrole with aldehyde. Recently, several methods have been developed, for the synthesis of dipyrromethanes in various catalyst such as ionic liquid [Hmim] BF$_4$ [9], HCl/water [10], cation exchange resin [11], metal triflate catalysis [12], HCl [13], iodine/CH$_2$Cl$_2$ [14] and InCl$_3$ [15]. However, all of the synthetic protocols

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reported so far suffer from disadvantages such as, use of metal [12], expensive reagent [11], prolonged reaction time[13], use of organic solvent [14], harsh reaction condition [13], use of excess pyrrole [12] and low yield [9]. Because of that, the researcher still continuous to have a better methodology for the synthesis of dipyrromethanes in terms of simplicity, eco-friendly, economic viability, high yielding at lowest pyrrole/aldehyde ratio which is achieved by using stannous chloride dehydrate.

In recent years, SnCl₂·2H₂O is frequently used in organic synthesis [16] as a catalyst due to its properties such as nontoxic nature, easy availability, inexpensive and easiness for work up. It played a great role for the synthesis of biologically active heterocycles such as benzimidazoles [17], quinoxalines [18] and functionalization of 4,5-diaminopyrazoles [19].

**Material and Methods**

Purity of the compounds was checked by thin layer chromatography (TLC) on Merck silica gel 60 F254 pre-coated sheets. Melting points of the synthesized compounds were determined in open-glass capillaries on a stuart-SMP10 melting point apparatus. IR absorption spectra were recorded on a Perkin Elmer 1650 FTIR using KBr pellets in the range of 4,000-450 cm⁻¹. ¹H-NMRs were recorded on a Bruker spectrometer operating at 400 MHz. The ¹H-NMR chemical shifts are reported as parts per million (ppm) downfield from TMS (Me₄Si) used as an internal standard. Mass spectra were recorded on LCQ ion trap mass spectrometer. All compounds were known, and obtained physical and spectroscopic data were compared with literatures data.

**General procedure**

A mixture of pyrrole (2 mmol), aldehyde (1 mmol) and SnCl₂·2H₂O (0.2 mmol) was crushed in a mortar with a pestle at room temperature. Progress of reaction was monitored by TLC. After completion of reaction (< 1 min) the crude product was washed with water, dried and purified by column chromatography using silica gel with petroleum ether/chloroform as the eluent. Pure products were obtained as solids.

5-(4-nitrophenyl)dipyrromethane: Yellow powder; mp: 159–160 °C, IR (KBr) 3394, 3360, 3100, 1597, 1516, 1348, 1120, 1025, 807, 737, 660, 565 cm⁻¹; ¹H NMR(400 MHz, CDCl₃): δ 5.58 (s, 1H, mesoH), 5.85 (br s, 2H, 2C₃–H), 6.16 (dd, J = 5.7, 2H, 2C₄–H), 6.74 (dd, J = 2.8, 4.2, 2H, 2C₅–H), 7.36 (d, J = 8.6, 2H, H-Ar), 8.0 (br s, 2H, N–H), 8.15 (d, J = 8.8, 2H, Ar-H).; MS (ES) Found [Calcld.]: m/z 267.30 [267.28] (MH⁺).

5-(2-Nitrophenyl)dipyrromethane (1): Brown oily liquid; IR (KBr) 3402, 1602, 1534, 1340, 1029, 815, 730, 661, 567 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 5.87 (s,
1H, mesoH), 6.11–6.24 (m, 4H), 6.65–6.70 (m, 2H), 7.24–7.55 (m, 3H), 7.87–7.90 (m, 1H), 8.18 (brs, 2H, NH); MS (ES) Found [Calcd.]: m/z 267.26 [267.29] (MH⁺).

5-(4-Fluorophenyl)dipyrromethane (2): brown crystals; mp: 80–81 °C, IR (KBr) 3416, 2930, 1608, 1496, 1450, 1287, 1174, 1100, 964, 764, 558 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 5.47 (s, 1H, mesoH), 5.88 (br s, 2H, 2C3-H), 6.17 (dd, J 2.7, 5.8, 2H, 2C4-H), 6.67 (br s, 2H, 2C5-H), 7.02–7.07 (m, 2H, Ar-H), 7.18–7.24 (m, 2H, Ar-H), 7.80 (br s, 2H, 2N-H); MS (ES) Found [Calcd.]: m/z 240.15 [240.27] (MH⁺).

5-Phenyldipyrromethane (3): Pale yellow crystals; mp: 100 °C, IR (KBr) 3448, 2950, 1634, 1512, 1412, 1291, 1227, 1048, 761, 704, 607 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 5.47 (s, 1H, mesoH), 5.94 (br s, 2H, 2C3-H), 6.14 (dd, J 2.8, 5.8, 2H, 2C4-H), 6.67 (dd, J 2.6, 4.2, 2H, 2C5-H), 7.20–7.37 (m, 5H, Ar-H), 7.87 (br s, 2H, 2N-H); MS (ES) Found [Calcd.]: m/z 222.31 [222.28] (MH⁺).

5-(4-Methoxyphenyl)dipyrromethane (4): Pale yellow powder; mp: 98–99 °C, IR (KBr) 3407, 2965, 2934, 1615, 1507, 1455, 1298, 1246, 1174, 1105, 1025, 964, 837, 775, 722, 554 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.80 (s, 3H, OCH₃), 5.44 (s, 1H, mesoH), 5.90–5.93 (m, 2H, 2C3-H), 6.16 (dd, J 2.8, 5.7, 2H, 2C4-H), 6.64–6.68 (m, 2H, 2C5-H), 6.87 (d, J 8.4, 2H, Ar-H), 7.16 (d, J 8.4, 2H, Ar-H), 7.80 (br s, 2H, 2N-H); MS (ES) Found [Calcd.]: m/z 252.33 [252.31] (MH⁺).

5-(2,6-Dichlorophenyl)dipyrromethane (5): Yellow solid. mp 102–103 °C, IR (KBr) 3412, 2925, 1612, 1495, 1447, 1282, 1175, 1101, 792, 741, 529 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 6.08 (s, 1H, mesoH); 6.15 (dd, J 2.4, 5.4 Hz, 2H); 6.49 (s, 1H); 6.70–6.71 (m, 2H), 7.14 (t, J 8.0 Hz, 2H), 7.30 (d, J 8.0 Hz, 2H), 8.29 (bs, 2H, NH); MS (ES) Found [Calcd.]: m/z 291.21 [291.17] (MH⁺) 293.15 (MH⁺²).

5-(4-Methylphenyl)dipyrromethane (6): Pale yellow crystals; mp: 110 °C, IR (KBr) 3415, 2356, 1634, 1509, 1425, 1253, 1090, 1024, 964, 908, 791, 745, 506 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.35 (s, 3H, CH₃), 5.45 (s, 1H, mesoH), 5.90 (br s, 2H, 2C3-H), 6.15 (dd, J 2.7, 5.8, 2H, 2C4-H), 6.64 (dd, J 2.5, 4.0, 2H, 2C5-H), 7.10–7.14 (m, 4H, Ar-H), 7.84 (br s, 2H, 2N-H); MS (ES) Found [Calcd.]: m/z 236.28 [236.31] (MH⁺).

5-(4-Chlorophenyl)dipyrromethane (7): Pale yellow powder; mp: 112–114 °C, IR (KBr) 3380, 2960, 2922, 2860, 1642, 1487, 1405, 1250, 1085, 1018, 765, 722, 554, 507 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 5.40 (s, 1H, mesoH), 5.88 (br s, 2H, 2C3-H), 6.15 (dd, J 2.8, 5.6, 2H, 2C4-H), 6.67 (dd, J 2.7, 4.2, 2H, 2C5-H), 7.14 (d, J 8.1, 2H, Ar-H), 7.30 (d, J 8.1, 2H, Ar-H), 7.82 (br s, 2H, 2N-H); MS (ES) Found [Calcd.]: m/z 256.75 [256.73] (MH⁺), 257.74 (MH⁺²).

5-(4-Bromophenyl)dipyrromethane (8): yellow powder; mp: 123–124 °C, IR
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(KBr) 3372, 3096, 2958, 2922, 2860, 1705, 1484, 1404, 1081, 1020, 767, 721, 645, 545, 502 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 5.40 (s, 1H, mesoH), 5.92 (br s, 2H, 2C3-H), 6.15 (dd, J 2.7, 5.6, 2H, 2C4-H), 6.66 (dd, J 2.5, 4.2, 2H, 2C5-H), 7.12 (d, J 8.2, 2H, Ar-H), 7.45 (d, J 8.2, 2H, Ar-H), 7.81 (br s, 2H, 2N-H); MS (ES) Found [Calcd.]: m/z 301.15 [301.18] (MH⁺).

Results and Discussion

We began our study by grinding the mixture of 2 mmol pyrrole and 1 mmol 4-nitrobenzaldehyde (Scheme 1) under the reaction conditions described in Table 1.

![Scheme 1. Synthesis of 5-(4-nitrophenyl)dipyrromethane.](image)

Initially, the mixture was ground in mortar with a pestle at room temperature under neat condition. However, result demonstrated the need of catalyst since the starting material was recovered (Entry 1). Thus, we chose 0.1 mmol SnCl₂·2H₂O as a catalyst. The result demonstrated that stoichiometric use of SnCl₂·2H₂O gives moderate yield of the product (Entry 2). The excellent yield was obtained at 0.2 mmol of SnCl₂·2H₂O (Entry 3) which is greater than that of 0.3 mmol of SnCl₂·2H₂O as a catalyst (entry 4). For evaluating the amount of catalyst, SnCl₂·2H₂O was employed in 0.4 and 0.5 mmol, however result demonstrated that moderate yield of product (Entry 5 and 6). Thus, from all above data, we confirmed that reaction gives excellent yield at 0.2 mmol of SnCl₂·2H₂O. This study also confirmed that the SnCl₂·2H₂O played a great role as a Lewis-acid catalyst because its absence did not give desired product (Entry 1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>SnCl₂·2H₂O (mmol)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.0</td>
<td>20</td>
<td>00b</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>2</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
<td>&lt; 1</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>0.3</td>
<td>&lt; 1</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>0.4</td>
<td>&lt; 1</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>0.5</td>
<td>&lt; 1</td>
<td>78</td>
</tr>
</tbody>
</table>

* isolated yield of the products. bThe starting material was recovered.
Another interesting result in this article was found that we got excellent yield at lowest pyrrole/aldehyde ratio i.e. 2:1. This result was compared with the literatures best pyrrole/aldehyde ratio (Table 2). In these Littler et al [7c] and Naik et al [11] afforded moderate yield at high pyrrole/aldehyde ratio (Entry 2 and 3). Faugeras et al [14] gave good yield of the product but they had done their work at high pyrrole/aldehyde ratio (Entry 4). Rohand et al [13] also carried out a good job but they did not try at lowest pyrrole/aldehyde ratio (Entry 1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Pyrrole/aldehyde ratio</th>
<th>Yielda (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HCl</td>
<td>3:1</td>
<td>97 [13]</td>
</tr>
<tr>
<td>2</td>
<td>TFA</td>
<td>25:1</td>
<td>56 [7c]</td>
</tr>
<tr>
<td>3</td>
<td>Cation exchange resin (T-63)</td>
<td>20:1</td>
<td>61 [11]</td>
</tr>
<tr>
<td>4</td>
<td>I₂, CH₂Cl₂</td>
<td>10:1</td>
<td>84 [14]</td>
</tr>
<tr>
<td>5</td>
<td>SnCl₂ 2H₂O</td>
<td>2:1</td>
<td>98</td>
</tr>
</tbody>
</table>

*a*Isolated yield of the 5-(4-nitrophenyl)dipyrromethane.

Thus, from above data, it was cleared that none of the above best literatures can be compared with our best results i.e. use of low pyrroloaldehyde ratio and excellent yield of the product.

In order to confirm these interesting results, we applied this method to the synthesis of various meso-substituted dipyrromethanes (Scheme 2) and obtained results were compared with literature best methods (Table 3).

![Scheme 2. Synthesis of various meso-substituted dipyrromethanes.](image)

Table 3 cleared that there was no influence of the electronic nature of the substituent on the reaction time or yield. Thus, it is possible to affirm that aldehydes containing electron donating or withdrawing groups reacted well in very short time (< 1 min) and gave corresponding dipyrromethanes in excellent yield (92-97%) as compared to best method found in literatures. In the case of 5-(4-metoxyphenyl)dipyrromethane, Faugeras et al. [14] gave excellent yield (90 %) in short reaction time but they performed their work by using dichloromethane as a solvent and by using microwave oven, which is always harmful to the environment and have economically higher cost. In
the another case of 5-phenyldipyrromethane and 5-(2,6-dichlorophenyl)dipyrromethane, Rohand et al. [13] gave good yields (86 and 85 %) in prolonged reaction time but they performed their work by using large quantity of strong acid which is always hazardous to the environment.

Table 3: Comparison of the yields with best methods found in the literatures

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Isolated Yield (%) /Pyrrole:aldehyde ratio</th>
<th>Literature best yield (%) /Pyrrole:aldehyde ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>4-fluorobenzaldehyde</td>
<td>95/2:1</td>
<td>77/20:1 [11]</td>
</tr>
<tr>
<td>3</td>
<td>Benzaldehyde</td>
<td>97/2:1</td>
<td>86/03:1 [13]</td>
</tr>
<tr>
<td>4</td>
<td>4-methoxybenzaldehyde</td>
<td>94/2:1</td>
<td>90/10:1 [14]</td>
</tr>
<tr>
<td>5</td>
<td>2,6-Dichlorobenzaldehyde</td>
<td>95/2:1</td>
<td>85/03:1 [13]</td>
</tr>
<tr>
<td>6</td>
<td>4-methybenzaldehyde</td>
<td>95/2:1</td>
<td>83/40:11 [12]</td>
</tr>
<tr>
<td>7</td>
<td>4-chlorobenzaldehyde</td>
<td>97/2:1</td>
<td>77/20:1 [11]</td>
</tr>
<tr>
<td>8</td>
<td>4-bromobenzaldehyde</td>
<td>92/2:1</td>
<td>74/40:11 [12]</td>
</tr>
</tbody>
</table>

*products were characterized by IR, 1H·NMR, MS (ES) and coincided with literature data, *pyrrole/imine ratio instead ofpyrrole/aldehyde ratio.

Thus, from all above results and discussion it was cleared that this method is superior in terms of use of inexpensive catalyst, solvent free reaction, lowest pyrrole/aldehyde ratio, very short reaction time and excellent yield of the products.

**Conclusion**

In conclusion, we have discovered highly rapid and simple method for the quantitative synthesis of meso-substituted dipyrromethanes at lowest pyrrole/aldehyde ratio and by using SnCl₂·2H₂O as a catalyst. The use of this nontoxic, easily available and inexpensiveness catalyst make this protocol practical and economically attractive.

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**References and Notes**


